PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
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Serial No.: 09/929,381 (Conf. #1047)

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For: METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

Group Art Unit: 1614

Examiner: R. Cook

Atty. Dkt. No.: 1973 US

CERTIFICATE OF MAILING
37 C.F.R 1.8

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March 20, 2006 Barbara McKenzie
Date Barbara McKenzie

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper provides an Appeal Brief in response to the Final Office Action dated August 18, 2005, for which the three-month date for response was November 18, 2005. A Response to the Final Office Action, along with a Notice of Appeal, was timely filed on November 18, 2005. An Advisory Action maintaining the rejections, and stating that the amendments made in the Response to Final Action would not be entered, was mailed on January 9, 2006. The due date for the Appeal Brief was January 18, 2006.

A request for a two-month extension of time to file this Appeal Brief is included herewith along with the required fee. This two-month extension will bring the due date to March 20, 2006 (by virtue of March 18, 2006, being a Saturday and March 19, 2006, being a

Sunday), which is within the six-month statutory period for filing of an Appeal Brief. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Alcon, Inc. Deposit Account No. 501051.

I. REAL PARTY IN INTEREST

The real party in interest in this case is Alcon, Inc., by virtue of assignment from the inventors to Alcon, Inc., as evidenced in the assignment document attached hereto in the Evidence Appendix.

II. RELATED APPEALS AND INTERFERENCES

Applicants know of no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-9 were originally filed with the case. Claim 1 was amended in response to an Official Action mailed May 20, 2004. Claims 1, 3, and 5-8 were amended and claim 4 was canceled in response to an Official Action mailed January 7, 2005. No claims were amended, added or canceled in the Response to Final Office filed on November 18, 2005. Claim 1 is amended and claim 9 is canceled in an amendment accompanying this Appeal Brief.

An Advisory Action mailed January 9, 2006, states that the arguments made in response to the Final Office Action did not place the application in condition for allowance.

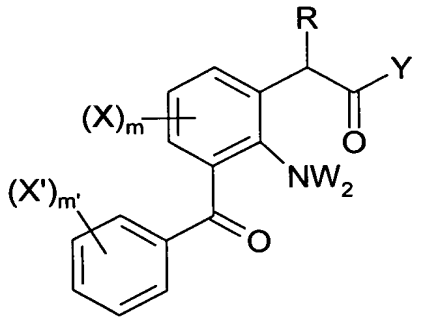
Thus, claims 1-3 and 5-8 are the subject of this Appeal. The Appealed claims are set forth the Claims Appendix.

IV. STATUS OF AMENDMENTS

Claim 1 is amended and claim 9 is canceled in the amendment accompanying this paper.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a method of treating an ophthalmic angiogenesis-related disorder by administering a therapeutically effective amount of 3-benzoylphenylacetic acid, or a derivative thereof having the described formula. The methods of the present invention are accomplished by administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or derivative of the formula:



wherein

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),

$-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);
A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), —$(CH_2)_nOR^3$;
R" = H, OH, OR';
X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;
R^4 = C_{1-6} (un)branched alkyl;
m = 0-3;
m' = 0-5; and
w = O, H.

(Specification page 3, lines 1-23).

In preferred aspects, the compounds for use in the present invention include those where R is H or C_{1-2}alkyl; Y is NR'R", R' is H, C_{1-6}(un)branched alkyl, or —$(CH_2)_nZ(CH_2)_{n'}A$; Z is nothing, O, $CHOR^3$, or NR^3; R^3 is H; A is H, OH, (un)substituted aryl (wherein the substitution is defined by X); X and X' are independently chosen from H, F, Cl, Br, CN, CF_3, OR', SR^4, or R^4; R" is H; R^4 is C_{1-4} (un)branched alkyl; m is 0-2; m' is 0-2; W is H; n is 2-4; and n' is 0-3. (Spec. page 4, lines 1-18).

The preferred compounds for use in the compositions or methods of the present invention are 2-amino-3-benzoyl-phenylacetamide (nepafenac), 2-amino-3-(4-chlorobenzoyl)-phenylacetamide, and 2-amino-3-(4-fluorobenzoyl)-phenylacetamide. (Spec. page 4, lines 20-23). The most preferred compound for use in the methods of the invention is 2-amino-3-benzoyl-phenylacetamide (nepafenac).

Generally, the patient whose ophthalmic angiogenesis-related disorder is treated is suffering from a disorder such as exudative macular degeneration, proliferative diabetic retinopathy, ischemic retinopathy, retinopathy of prematurity, neovascular glaucoma, iritis

rubeosis, corneal neovascularization, cyclitis, sickle cell retinopathy or pterygium. (Spec. page 4, line 31 to page 5, line 2).

The compositions for use in the methods of the present invention can be administered in a variety of ways, including all forms of local delivery to the eye, such as subconjunctival injections or implants, intravitreal injections or implants, sub-Tenon's injections or implants, incorporation in surgical irrigating solutions, etc. (Spec. page 5, lines 8-11).

The doses of the compositions used in the methods of the present invention will generally depend upon the type of disorder to be prevented or treated, the age and body weight of the patient, and the form of preparation/route of administration. Preferred compositions intended for ophthalmic administration will typically contain a compound of formula I in an amount of from about 0.001 to about 4.0% (w/v). (Spec. page 6, lines 1-10).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. **Is claim 9 definite within the meaning of 35 U.S.C. § 112, second paragraph?**

2. **Are claims 1-3 and 5-8 obvious under 35 U.S.C. § 103(a) over Bayly *et al.* or Kalgutkar *et al.* in view of Hellberg *et al.*?**

VII. ARGUMENT

A. The Definiteness Rejection as Applied to Claim 9 is Moot

The Advisory Action states that the rejection under §112, second paragraph to claim 9 was not addressed in the Response to Final Office Action filed on November 18, 2005. The rejection in the Final Office Action states that claim 9 is indefinite because none of the disorders recited are ophthalmic angiogenesis-related disorders. Claim 9 is canceled in an

amendment accompanying this Appeal Brief, therefore, it is believed that the indefiniteness rejection of claim 9 is moot.

B. The Claims Are Patentable over Bayly or Kalgutkar in view of Hellberg

The Final Action rejects all claims as being unpatentable over Bayly (U.S. Patent No. 5,994,379) or Kalgutkar in view of Hellberg (U.S. Patent 6,342,524). Bayly is said to disclose that diabetic retinopathy and tumor angiogenesis are cyclooxygenase-mediated proliferative disorders and to further disclose the recited routes of administration. Kalgutkar is said to disclose that COX-2 inhibitors are antiangioangenic and antitumorigenic. The Action acknowledges that the claimed invention differs from Bayly and Kalgutkar in reciting a compound that is a derivative of the compounds disclosed in Kalgutkar. Hellberg is said to disclose that the recited compounds are COX inhibitors and to further disclose ophthalmic administration. Applicants respectfully traverse.

The present invention is the first to show that nepafenac and related compounds can be used to treat an ophthalmic angiogenesis-related disorder. The compounds disclosed in Bayly differ vastly from the compounds disclosed for use in the methods of the present invention. For example, all of the compounds described and illustrated in Bayly contain two 6-membered aromatic or non-aromatic rings connected by a single carbon-carbon bond. The compounds described for use in the methods of the present invention contain two 6-membered aromatic rings wherein the connection between the rings includes a C=O. There is no suggestion within Bayly to modify the compounds described therein to contain a C=O in the connection between the aromatic rings, for use in treating a COX-2 mediated disease.

Kalgutkar discusses the use of certain secondary amides of certain NSAIDs to treat cancer. It is important to note that, Kalgutkar focuses only on the treatment of cancer. There is no discussion or suggestion within Kalgutkar to use the described secondary amides to treat

ophthalmic angiogenesis-related disorders. The Final Action maintains the rejection based on Kalgutkar, stating only that "Kalgutkar discloses the instant amide compounds." In short, the Final Action does not provide an explanation of what it believes to be the motivation for using the compounds described in Kalgutkar to treat ophthalmic disorders.

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

There is no suggestion or motivation within Hellberg to administer the compounds of the present invention by themselves for the sole purpose of treating angiogenesis-related disorders. The focus of the invention of Hellberg is to lower IOP by administering a combination of compounds. The remainder of the description of the problem and the solution provided in Hellberg focuses on the increase of ocular hypertension caused by glucocorticoid induction of the

GLC1A protein. This is what Hellberg seeks to treat. Furthermore, there is no motivation found within Hellberg, Bayly or Kalgutkar to combine the teachings therein.

Hellberg discusses the use of certain compounds to treat GLC1A glaucoma and does not discuss the treatment of angiogenesis-related disorders at all. The Final Action states that Hellberg is relevant in that it disclosed the instant compound is a COX-2 inhibitor, and further discloses ophthalmic administration and the instant dosage. Unfortunately, the Final Action seems to disregard the remainder of Hellberg for what it teaches regarding glaucoma and the use of non-steroidal anti-inflammatory agents in its treatment. This amounts to a "picking and choosing" of certain parts of the reference while ignoring other aspects of it.

The Federal Circuit has held that "it is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference *fairly suggests* to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (CCPA 1965)). Hellberg discusses extensively the relationship of the GLC1A gene to the occurrence of glaucoma. The GLC1A gene encodes a 57 kD protein that is expressed in the trabecular meshwork (TM) (col. 2, lines 20-21). The expression of this protein is upregulated by glucocorticoids (col. 2, lines 23-25). The glucocorticoid induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma. (col. 2, lines 32-35). It is this effect, the increase in ocular hypertension caused by glucocorticoid induction of the GLC1A protein, that Hellberg seeks to treat.

Hellberg discusses the mechanism by which the glucocorticoid induction of the GLC1A protein causes an increase in ocular hypertension, or intraocular pressure (IOP). It states, in pertinent part:

> It is known that the trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton [ ] and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, *the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises.* If this state of elevated intraocular pressure (IOP) is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field.

(col. 3, lines 16-37, *citations omitted, emphasis added*). Hellberg's objective is to decrease the IOP in glaucoma patients suffering from an increased IOP due to glucocorticoid induction of the expression of the GLC1A gene. Hellberg does not discuss the administration of derivatives of 3-benzoylphenylacetic acid to treat angiogenesis-related disorders. In fact, Hellberg discusses the use of such compounds only in combination with a prostaglandin for the treatment of GLC1A glaucoma. Hellberg does not discuss the use of derivatives of 3-benzoylphenylacetic acid by themselves to treat angiogenesis-related disorders.

The purpose of the presence of non-steroidal cyclooxygenase inhibitors in the combinations of Hellberg is to prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22). The prostaglandin in the compositions of Hellberg provides the "acute effect" for lowering IOP. The non-steroidal cyclooxygenase inhibitors, used in combination with the prostaglandins, are present to ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering. (col. 5, lines 28-35).

Clearly, Hellberg's objective is to treat GLC1A glaucoma by lowering IOP, not to directly treat angiogenesis-related disorders.

The Action appears to be ignoring what Hellberg *fairly suggests* to one skilled in the art." *Bausch & Lomb*, 230 U.S.P.Q. at 419. As discussed above, Hellberg suggests to the skilled artisan that the administration of derivatives of 3-benzoylphenylacetic acid in combination with a prostaglandin will prevent the expression of GLC1A and thereby prevent the development of ocular hypertension or increased IOP. (col. 5, lines 20-22).

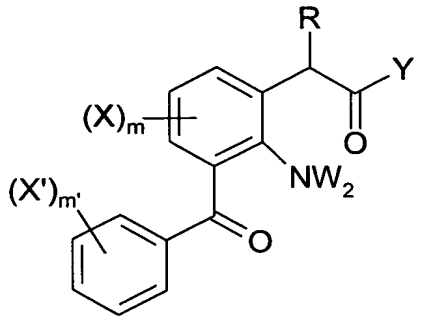
In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection based on Hellberg in combination with Bayly or Kalgutkar be withdrawn.

C. A Terminal Disclaimer is Included With This Paper

Finally, the Advisory Action acknowledges that a Terminal Disclaimer to overcome the double patenting rejections have not been filed. Applicants stated in the Response to Final Office that such Terminal Disclaimers would be filed "when appropriate." In order to expedite allowance of the case and to simplify the issues for Appeal, Applicants include a Terminal Disclaimers relating to co-pending U.S.S.N. 10/344,881 with this paper. A Terminal Disclaimer relating to U.S.S.N. 10/417,466 will not be filed because that case has been abandoned.

VIII. CLAIMS APPENDIX

1. (currently amended) A method of treating an ophthalmic angiogenesis-related disorder in a patient suffering from such a disorder which comprises administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or a derivative thereof ~~of~~having the following formula:



wherein

R = H, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),

$-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_n2$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $—(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_n2R^4$, CF_3, R^4, NO_2;

R^4 = C_{1-6} (un)branched alkyl;

m = 0-3;

m' = 0-5; and

W = O, H.

2. (original) The method of Claim 1 wherein

R = H, C_{1-2} alkyl;

Y = NR'R"

R' = H, C_{1-6} (un)branched alkyl, --$(CH_2)_nZ(CH_2)_{n'}A$;

Z = nothing, O, $CHOR^3$, NR^3;

R_3 = H;

A = H, OH, (un)substituted aryl (substitution as defined by X below);

X and X' independently = H, F, Cl, Br, CN, CF_3, OR', SR^4, R^4;

R" = H;

R^4 = C_{1-4} (un)branched alkyl;

m = 0-2;

m' = 0-2;

W = H;

n = 2-4; and

n' = 0-3.

3. (previously presented) The method of Claim 2 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. (canceled)

5. (previously presented) The method of Claim 1 wherein the 3-benzoylphenylacetic acid or derivative thereof is topically administered to the eye.

6. (previously presented) The method of Claim 5 wherein the therapeutically effective amount of 3-benzoylphenylacetic acid or derivative thereof is from about 0.001 to about 4.0% (w/v).

7. (previously presented) The method of Claim 1 wherein the angiogenesis-related disorder is selected from the group consisting of exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy; retinopathy of prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium.

8. (previously presented) The method of Claim 1 wherein the 3-benzoylphenylacetic acid or derivative thereof is administered orally, intravenously, in a subconjunctival injection or implant, in a sub-Tenon's injection or implant, in an intravitreal injection or implant, or in a surgical irrigating solution.

9. (canceled)

IX. EVIDENCE APPENDIX

Evidence of assignment of the invention to Alcon, Inc. is attached behind this page.

X. RELATED PROCEEDINGS APPENDIX

None.

This is submitted to be a complete Brief on Appeal.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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